

Inventor: Indu Parikh
U.S. Serial No.: 09/282,471
Filing Date: March 31, 1999

Attorney Docket No.: 28069-547CIP2
(Formerly: 401865/SKYE PHARMA)

Listing of Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1.-32. (Canceled)

33. (Currently Amended) A method of preparing fenofibrate microparticles, ~~including a particle size reduction process for reducing the initial average particle size which includes reducing the initial average particle size by sonication, milling, homogenization, microfluidization, antisolvent and solvent precipitation, or a combination thereof,~~ the method comprising the steps of:

- (1) mixing the fenofibrate particles with (a) a natural or synthetic phospholipid and (b) at least one non-ionic, anionic, or cationic surfactant to form a mixture, prior to or during the ~~reduction of particle size reduction process~~; and thereafter
- (2) applying energy to the mixture sufficient to produce fenofibrate microparticles having a volume-weighted mean particle size that is about 50% smaller than particles produced without the presence of the surfactant using the same energy input.

34. (Currently Amended) The method [of] according to claim 33, wherein step (1) further comprises: mixing the fenofibrate particles with (a) at least two phospholipids and at least one surfactant, (b) a phospholipid and at least two surfactants, or (c) at least two phospholipids and at least two surfactants.

35. (Currently Amended) The method [of] according to claim 33, wherein the mixture comprises an alkyl aryl polyether sulfonate, a sorbitan fatty acid ester, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene stearate, a polyethylene glycol, benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, or a combination of any thereof.

36. (Currently Amended) The method [of] according to claim 33, wherein the

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phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, sphingomyelin, dimyristoyl ~~phosphatidylglycerol~~ ~~phosphatidylglycerol~~ sodium salt, phosphatidic acid, lysophospholipids and combinations thereof.

37. (Canceled)

38. (Currently Amended) The method [of] according to claim 33, wherein the fenofibrate ~~particles~~ ~~microparticles~~ are 5-100 μ m in size, ~~such that the said fenofibrate microparticles have~~ having a volume-weighted mean particle size value that is about 80% smaller than particles produced without the presence of the surfactant using the same energy input.

39. (Currently Amended) The method [of] according to claim 33, wherein the mixture comprises a surfactant in a concentration above its critical micelle concentration.

40. (Currently Amended) The method [of] according to claim 33, wherein the method comprises preparing a pharmaceutically acceptable composition from the composition of fenofibrate microparticles.

41. (Currently Amended) The method [of] according to claim 40, wherein the method comprises preparing a suspension of the fenofibrate microparticles.

42. (Currently Amended) The method [of] according to claim [41] ~~40~~, wherein the method comprises preparing a powder from the composition by lyophilization, fluid drying, or spray drying.

43. (Withdrawn) The method of claim 42, wherein the method comprises preparing an orally administrable gel capsule comprising the powder.

44. (Withdrawn) The method of claim 42, wherein the method comprises preparing an orally administrable granule from the powder.

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45. (Currently Amended) The method [of] ~~according to~~ claim 42, wherein the method comprises preparing an orally administrable tablet ~~from comprising~~ the powder.
46. (Currently Amended) The method [of] ~~according to~~ claim [42] 40, wherein the composition is spray dried and the surfactant consists of polyvinylpyrrolidone, or a combination of ~~polyvinylpyrrolidone~~ polyvinylpyrrolidone and one or more additional surfactants.
47. (Currently Amended) The method [of] ~~according to~~ claim 46, wherein the composition is further converted into granules.
48. (Currently Amended) A composition comprising fenofibrate microparticles produced by the method [of] ~~according to~~ claim 33.
49. (Canceled)
50. (Currently Amended) A pharmaceutically acceptable composition comprising granules produced by the method [of] ~~according to~~ claim 47.
51. (Canceled)
52. (Currently Amended) The method [of] ~~according to~~ claim 33, wherein the surfactant is selected from the group consisting of casein, tragacanth, enteric resins, cholesterol esters, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, polyvinyl alcohol, polyvinylpyrrolidone, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively-charged glycerol esters, quaternary ammonium compounds, chitosans, colloidal clays, sodium dodecylsulfate, sodium deoxycholate, and combinations thereof.
- 53.-54. (Canceled)

55. (New) A method of preparing fenofibrate microparticles which includes reducing the initial average particle size by sonication, homogenization, milling, microfluidization, antisolvent and solvent precipitation, or a combination thereof, the method comprising the steps of:

- (1) mixing the fenofibrate particles with (a) a natural or synthetic phospholipid and (b) at least one non-ionic, anionic, or cationic surfactant to form a mixture, prior to or during the reduction of particle size, said surfactant being selected from one or more of casein, tragacanth, enteric resins, cholesterol esters, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, polyvinyl alcohol, polyvinylpyrrolidone, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively-charged glycerol esters, quaternary ammonium compounds, chitosans, colloidal clays, sodium dodecylsulfate, sodium deoxycholate, and combinations thereof; and thereafter
- (2) applying energy to the mixture sufficient to produce fenofibrate microparticles having a volume-weighted mean particle size that is about 50% smaller than particles produced without the presence of the surfactant using the same energy input.

56. (New) The method according to claim 55, wherein step (1) further comprises: mixing the fenofibrate particles with (a) at least two phospholipids and at least one surfactant, (b) a phospholipid and at least two surfactants, or (c) at least two phospholipids and at least two surfactants.

57. (New) The method according to claim 55, wherein the mixture comprises an alkyl aryl polyether sulfonate, a sorbitan fatty acid ester, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene stearate, a polyethylene glycol, benzalkonium chloride,

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cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, or a combination of any thereof.

58. (New) The method according to claim 55, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, sphingomyelin, dimyristoyl phosphatidylglycerol sodium salt, phosphatidic acid, lysophospholipids and combinations thereof.

59. (New) The method according to claim 55, wherein the fenofibrate microparticles are 5-100 μm in size, said fenofibrate microparticles having a volume-weighted mean particle size value that is about 80% smaller than particles produced without the presence of the surfactant using the same energy input.

60. (New) The method according to claim 55, wherein the mixture comprises a surfactant in a concentration above its critical micelle concentration.

61. (New) The method according to claim 55, wherein the method comprises preparing a pharmaceutically acceptable composition from the composition of fenofibrate microparticles.

62. (New) The method according to claim 61, wherein the method comprises preparing a suspension of the fenofibrate microparticles.

63. (New) The method according to claim 61, wherein the method comprises preparing a powder from the composition by lyophilization, fluid drying, or spray drying.

64. (New) The method according to claim 63, wherein the method comprises preparing an orally administrable tablet comprising the powder.

65. (New) The method according to claim 61, wherein the composition is spray dried and the surfactant consists of polyvinylpyrrolidone, or a combination of polyvinylpyrrolidone and one or more additional surfactants.

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66. (New) The method according to claim 65, wherein the composition is further converted into granules.

67. (New) A pharmaceutically acceptable composition comprising granules produced by the method according to claim 66.